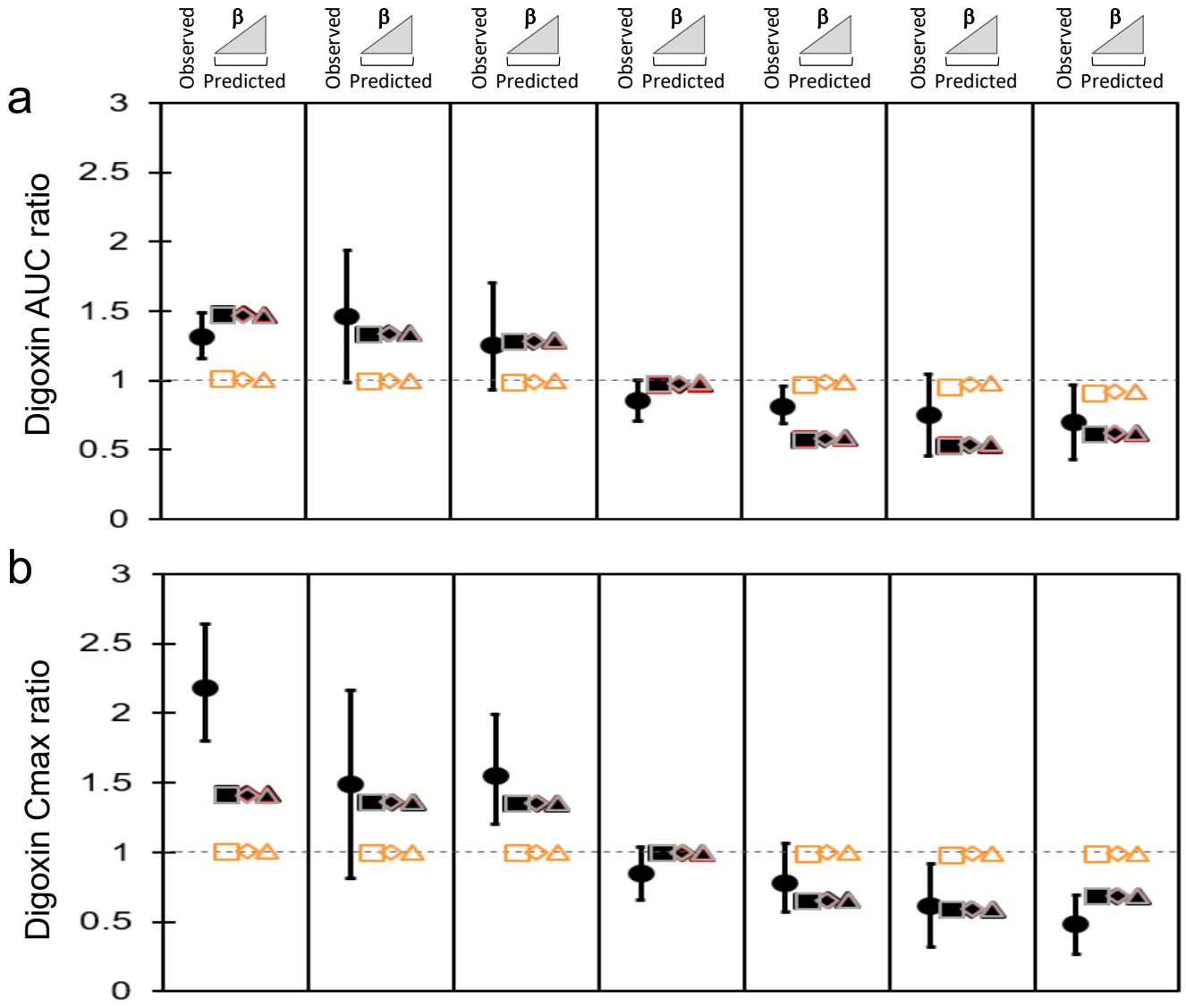

DIG dosing	0.25 mg (PO) (with RIF)	0.5 mg (PO) (1 h after RIF)	0.5 mg (PO) (with RIF)	1 mg (IV) (12 h after RIF)	0.5 mg (PO) (12 h after RIF)	0.25 mg (PO) (12 h after RIF)	1 mg (PO) (12 h after RIF)
RIF (PO) dosing	600 mg (Single dose)	600 mg QD (28 days)	600 mg QD (15 days)	600 mg QD (10 days)	600 mg QD (15 days)	300 mg BID (7 days)	600 mg QD (10 days)
Reference	Wiebe et al. (2020)	Reitman et al. (2011)	Kirby et al. (2012)	Greiner et al. (1999)	Kirby et al. (2012)	Gurley et al. (2008)	Greiner et al. (1999)

Figure S2 Predicted and observed AUC and Cmax ratios of digoxin with various dosing regimens of rifampicin. Closed circles represent observed digoxin AUCRs (a) and CmaxRs (b) shown as mean ± SD or mean (90% CI, first, third, and fifth boxes from the left). Predicted AUCRs (a) and CmaxRs (b) of digoxin are shown as mean in symbols of different shapes (squares, diamonds, and triangles for the hepatic β values of 0.2, 0.5, and 0.8, respectively). The closed black squares, diamonds, and triangles represent predicted AUCRs and CmaxRs by incorporating P-gp induction and inhibition effects of rifampicin in the intestine, liver, and kidney. In addition, to estimate the DDI impact in each tissue, the predicted AUCRs and CmaxRs of digoxin by not considering the intestinal, hepatic, or renal P-gp-mediated DDIs are shown in open orange, red, or gray symbols, respectively. Dosing regimens of digoxin and rifampicin are indicated at the bottom. AUCR, area under the plasma/blood concentration-time curve ratio; BID, twice daily; CmaxR, maximum plasma/blood concentration ratio; DIG, digoxin; IV, intravenous infusion dose; PO, oral dose; QD, once daily; RIF, rifampicin.